amino acid substituted. Claim 20 is drawn to a soluble tissue factor protein expressed from a nucleotide molecule encoding the amino acid sequence of Figure 2 from amino acid one to an amino acid residue between amino acid residues 219 and amino acid residue 263. Claim 31 is drawn to recombinant human tissue factor proteins expressed from a nucleotide sequence encoding an amino acid sequence which includes amino acids 1 to 219 as disclosed in Figure 2. Claim 41 is drawn to recombinant human tissue factor proteins which includes amino acids 1 to 219 as disclosed in Figure 2.

Rejections under 35 U.S.C. §112, first paragraph

Claims 4-6, 8, 20, 21, 23-25, 27-29, 31-36, and 38-41 were rejected under 35 U.S.C. §112, first paragraph, on the basis that the specification, as originally filed, does not reasonably convey to one skilled in relevant art that the inventors had possession of the claimed invention. This rejection is respectfully traversed.

The present rejection is based, essentially, on the contention that the specification does not describe what is claimed so as to reasonably convey to one skilled in the art that applicants were in possession of the claimed tissue factor proteins at the time the application was filed. The main arguments presented by the Examiner revolve around the lack of specific reference to specific tissue factor variants within the region spanning amino acids 219-263.

Residues 1-219 and 220-242/43 are adequately described by the specification.

Legal standard for support within an application

The standard regarding what is or is not supported by the specification has been clearly articulated as requiring the specification to convey with reasonable clarity to those skilled in the art that, as of the filing date sought, the inventor was in possession of the invention, i.e., whatever is now claimed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555 19 USPQ2d 1111, 1117

(Fed . Cir. 1991). MPEP § 2163.02 also describes the standard to be applied in determining if the written description requirement is satisfied. MPEP § 2163.02 reads, in pertinent part:

> Whenever the issue [of adequacy of the written description] arises, the fundamental factual inquiry is whether *a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed.* The subject matter of the claim *need not be described literally* (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement. (emphasis added).

Thus, the subject matter does not "need to be described literally", it merely needs to have been "conveyed to those skilled in the art." *Id.*

The application of the description requirement must be done on a "case by case basis." *Ralston Purina Co. v. Far-Mar-Co., Inc.* 772 F.2d 1570, 277 USPQ 177 (Fed. Cir. 1985). The issue in *Ralston Purina Co.* revolved around the type of disclosure that was necessary to support specific embodiments when only general ranges were disclosed in the application. For example, the patent at issue in *Ralston Purina Co.* contained the following claim limitations: 1. in excess of 212° F.; 2. at least about 212°F.; 3. substantially above 212° F.; 4. substantially in excess of 212° F.; and 5. into the range of 212° -310° F. *Ralston Purina Co. v. Far-Mar-Co., Inc.* 772 F.2d 1570 (Fed. Cir. 1985). The only support the priority disclosure provided was the statement "[a mixture] must be subjected to heat" and Example 1 provided the range: 212° - 380° F. The trial court found all of the claim limitations discussed above supported by the priority disclosure because expert testimony indicated that one of ordinary skill in the art would not consider 380° an upper limit, but rather would consider what ever temperature the material burned at to be the upper limit. In addition it was found that the range 212° -310° was adequately described because it involved nothing "more than . . . that which had been described earlier." Two important concepts can be identified in this Federal Circuit decision. First, the expert testimony as to what one of ordinary skill in the art would judge to be described is valid and powerful evidence as to

what the application truly does describe. Second, as long as one of ordinary skill in the art would recognize lower boundaries of some defined range as describing a lower limit, an open ended claim is sufficiently described if a naturally occurring inherent upper boundary would be understood by the ordinary skilled person.

The Examiner has misconstrued the Konigsberg Declaration

The Declaration under 37 C.F.R. 1.132 does not "confuse the issue" as asserted by the Examiner (page 5, Office Action mailed, June 8, 1998). The Examiner has misconstrued what the Konigsberg Declaration states and implies. The Konigsberg Declaration indicates that one of ordinary skill in the art at the time the application was filed would know that the transmembrane domain would bridge the extracellular regions and the cytoplasmic regions. Furthermore, Dr. Konigsberg goes on to state that those of skill in the art understood that the "extracellular domain could be used separately from both the transmembrane region and the cytoplasmic region." (Konigsberg Declaration at 3). Dr. Konigsberg sums up the knowledge of one of ordinary skill in the art at the time of the priority application by saying, "it is clear, those of skill in the art at the time would have understood, that deletion of the transmembrane region is equivalent to deletion of both the transmembrane region and cytoplasmic region, since the cytoplasmic domain serves no purpose in the absence of the transmembrane domain." (Konigsberg Declaration at 4).

Based on the above it is erroneous for the Examiner to imply that the Konigsberg Declaration states that the transmembrane domain and the cytoplasmic domains are the same. This implies that Dr. Konigsberg, an acknowledged expert in the field of recombinant proteins, would not understand that if one is referring to the structure of the transmembrane region this refers to the hydrophobic residues so described in the application. The Konigsberg Declaration stands for the proposition that once one of ordinary skill in the art knew the transmembrane

region existed and the cytoplasmic region was unnecessary, one of ordinary skill in the art would interpret a deletion of the transmembrane region to simply refer to a deletion of the *carboxy terminal portion* of the protein, from the start of the transmembrane region as referenced to the amino terminus of the protein, i.e. amino acid 220.

Konigsberg is not in contradiction with the Spicer et al., Scarpati et al., and Fisher et al. publications. The Examiner is respectfully directed to the fact that Konigsberg is the senior author on the Spicer et al., publication, and is likely to be in a better position than either the Examiner or the Applicants' Attorney to assess whether he is in contradiction with his own publication. Presumably Dr. Konigsberg was aware of the Spicer et al. publication prior to signing his Declaration under Rule 1.132 and has factored that publication into his analysis.

A protein variant described in reference to amino acid 219 is fully described in the application.

Claims 4-6, 8, 20-21, 23, 27-29, 31-36 and 38-41 are drawn to molecules that include at least the first 219 amino acid residues of human tissue factor. The first 219 amino acids are fully described in the application. As pointed out in the application and explained by the Konigsberg Declaration, human tissue factor consists of three domains. The middle domain is the transmembrane domain and consists of residues 220-242/243 as described in the application. As pointed out by the Konigsberg Declaration, one of ordinary skill in the art given this information would readily realize that there would be an amino terminal portion consisting of residues 1-219 and a carboxy terminal portion consisting of residues 243/244 to 263. Thus, a person of ordinary skill in the art would know that a fragment of amino acids 1-219 precedes the transmembrane domain region and that residue 243/244 follows the transmembrane domain region.

The Examiner has acknowledged that the transmembrane domain of residues 220 to 242/243 was "adequately described." (page 4 Office Action mailed July 24, 1998). The Examiner than goes on to say that the region 1-219 of the protein is not adequately described. Respectfully, this does not make logical since. The situation is much like saying, the applicant has described dark by reference to light, but then asserting that light itself is not described. What is dark? It is not light and vice versa. There is no way that one can describe dark without also eliciting in one listening to the description, an image of light. Likewise, a description of a transmembrane region, necessarily elicits, within one of ordinary skill in the art, the regions of the protein that the transmembrane domain is associated with. Upon description of the transmembrane domain one of ordinary skill in the art is compelled to think of the regions both on the amino terminus side of the transmembrane domain and on the carboxy terminus side of the domain. In fact, it is not possible to think of "only a transmembrane domain." For applicants to be in possession of the transmembrane domain they necessarily had to be in possession of the rest of the protein, within which the transmembrane domain resides.

Not only does the transmembrane domain itself necessarily define the rest of the protein regions to one of ordinary skill in the art, but the application as a whole does describe the region of 1-219. For example, in Figure 5 and the description of Figure 5 references to the transmembrane domain, and its position to the amino terminus end of the protein, and the various regions of the protein are specifically defined. Figure 5 does show a hydropathy profile as asserted by the Examiner, but this is irrelevant to the purpose for which the Figure is being relied upon. The fact that it is a hydropathy profile simply refers to the data used to separate the protein into the three domains: amino terminus, transmembrane domain, and carboxy terminus. The description of Figure 5 on page 9 of the application states, "The abscissa shows the amino

acid sequence beginning at the mature amino terminus." This coupled with the knowledge of the transmembrane region clearly indicates to one of ordinary skill in the art that the protein is divided into three regions, referenced by the amino terminus of the protein. Contrary to the Examiner's assertion, Figure 5 and the corresponding text do indicate to one of ordinary skill in the art, the amino terminus region of the protein is amino acids residues 1 to 219.

The Examiner is reminded that as discussed above the legal standard for description is what one of ordinary skill in the art would have understood to be described by the application. One of ordinary skill in the art, as declared by Dr. Konigsberg, would have understood the implications of the transmembrane domain, and would have understood that there were other regions bordering the transmembrane domain.

In addition to the above, contrary to the Examiner's assertion, the specification does indicate that deletions of the transmembrane domain are not considered to be limited to deletion of only the specific amino acids of the transmembrane domain. For example, in the first full paragraph on page 15, the specification states that "a major *class* of substitutional or deletional variants *are those involving* the transmembrane, i.e. hydrophobic or lipophilic, region of tissue factor protein" (emphasis added). This sentence clearly conveys that applicants contemplated deletion variants which include both the deletion of the transmembrane region and deletion of other amino acids.

The only rationale provided in the rejection in support of this conclusion is that tissue factor protein from amino acid 1 to 219 is not *explicitly* described.[1] However, as noted above and as acknowledged in the Office Action, such literal description is not required to satisfy the

[1]Applicants also dispute that the application fails to provide an explicit description (see discussion of Figure 5 above).

description requirement. All that is required is that the application reasonably convey to those of skill in the art that applicants were in possession of the claimed subject matter. The mere conclusory statement in the rejection does not outweigh the expert analysis and testimony to the contrary. Applicants submit that the un-rebutted evidence of record indicates that the application does convey that applicants were in possession of tissue factor protein from amino acid 1 to 219 at the time the application was filed.

Since the un-rebutted evidence of record indicates that the specification conveys to those of skill in the art that applicants were in possession of a tissue factor protein lacking the C-terminal region beyond amino acid 219, a claim to a tissue factor protein comprising amino acids 1 to 219 is supported by the specification within the meaning of the first paragraph of 35 U.S.C. § 112. In this regard, applicants note that there is no basis in the description requirement of 35 U.S.C. § 112 for limiting applicants to a tissue factor "consisting of" amino acids 1 to 219. Where a composition is adequately described in an application, applicants are entitled to claim the composition using open, "comprising" language. All aspects of the protein are known and adequately described in the application. The sequence of the region 1 to 219 is known, the sequence of the transmembrane domain is known, and the sequence of the carboxy terminus region is known. The function of the various regions is known. There is absolutely no legal basis for restricting the applicants to the "consisting" language.

In the case of claims 20-29, deletions "involving" the transmembrane region (see discussion above) clearly encompass deletions of less than the entire transmembrane region, since a deletion variant in which a part of the transmembrane region is deleted is clearly a deletion "involving" the transmembrane domain. The examiner should note that three groups independently and within three months of each other obtained the gene encoding human tissue

factor, determined that the transmembrane region could be deleted and that a truncation could be made at amino acid 219, or shortly thereafter, to yield a soluble protein.

Claim 24 is fully described in the application. Claim 24 is drawn to a tissue factor comprising the amino acid sequence shown in Figure 2 *wherein the cysteine residues are substituted with other amino acids.* Describing "cysteine residues substituted with other amino acids" would meet the description requirement. For example, on page 16:lines 14-16 describe the deletion of cysteine residues. On page 14 of the application, Table 1. specifically lists a serine substitution for cysteine as an exemplary substitution. Applicant has met the description standard as outlined in *Vas-cath* and is not required to do more. Applicant was in possession of the variants of claim 24.

Claim 25 is fully described in the application. Claim 25 is drawn to a tissue factor comprising the amino acid sequence shown in Figure 2 wherein the potential proteolysis sites are deleted by replacing the amino acids with glutaminyl or histidyl residues or deleting one of the basic residues. On page 16:lines 16-19, deletion or substitution of potential proteolysis sites by replacement with glutaminyl or histidyl residues is described. There can be no doubt that claim 25 is fully described in the application.

Examiner's assertion that protein variants of tissue factor are not enabled or described is contrary to case law and the information disclosed in the application.

Legal standard for protein variants.

The CCPA first addressed the issue of protein variants in *In re Fisher*, 427 F.2d 833 (CCPA, 1970). Claim 4 of the Fisher application was drawn to preparations of adrenocorticotrophic hormone (ACTH) that had at least 1 unit of ACTH per milligram and contained at least 24 specific amino acids, known to be a part of ACTH. The court held that the

priority specification, which specifically recited ACTH preparations containing 39 amino acids, but did not specifically recite any ACTH variation containing other than 39 amino acids, did not enable a claim that included other than 39 amino acids. Integral to this holding was the court's reliance on the knowledge of one of ordinary skill in the art, and the lack of a showing that one of ordinary skill in the art could obtain sequences other than 39 amino acids long. The court stated,

> The parent specification does not enable one skilled in the art to make or obtain ACTHs with other than 39 amino acids in the chain, and *there has been no showing that one of ordinary skill would have known how to make or obtain such other ACTHs without undue experimentation.* As for Appellant's conclusion that the 25th to 39th acids in the chain are unnecessary, *it is one thing to make such a statement when persons skilled in the art are able to make or obtain ACTH having other than 39 amino acids*; it is quite another thing when they are not able to do so.

Id. at 836. (emphasis added).

It is clear that the court was placing great emphasis on what one of ordinary skill in the art could have hoped to make or obtain. This decision was handed down in 1970, on an application filed November 29, 1960, claiming priority from an application filed in 1949. The priority application was filed four years before Watson and Crick determined that the structure of DNA was a double helix (Watson and Crick *Nature* 171, 964-967 (1953)). It would still take 11 years of research before scientists even knew that there was a triplet code between a DNA sequence and a protein sequence (Crick et al. *Nature* 192 1227-1232 (1961)). It is not reasonable to assume that a holding, based on an application filed in 1954, prior to the advent of biotechnology, is controlling on biotechnology itself. The court in *In re Fisher* very likely correctly held that "one could not make or obtain", without undue experimentation, a protein with less than 39 amino acids . . . *in 1954*. The court just as correctly noted though that if one of

ordinary skill in the art could have made or obtained such a protein then the holding would have been very different.

The court in *Amgen, inc. v. Chugai Pharmaceutical Co., LTD.*, 927 F.2d 1200 (Fed. Cir. 1991) relied heavily on the holding in *In re Fisher* to find a claim drawn to a large number of non-natural Erythropoietin (EPO) analogs invalid for failing to meet the requirements of 35 U.S.C. 112. The court focused on the number of possible analogs that were encompassed by the claim **and** on the uncertainty held by the applicant as to which analogs, already produced, possessed the activity. The trial court relied on expert testimony which provided that "Amgen is still unable to specify which analogs have the biological properties set forth in the claim." *Id.* at 1213. The Federal Circuit chose to focus on the making and using of the DNA sequences, which encode the protein which has the biological activity, rather than the biological activity itself. While the *Amgen* court spoke positively of *In re Angstadt*, 537 F.2d 498, 502, which held that it is not necessary that a patent applicant test all embodiments of his invention just that he provide a sufficient disclosure to enable one skilled in the art to practice the full scope of the claims, they stated that for claims based on DNA sequences a sufficient disclosure meant, "disclosing how to make and use enough sequences to justify grant of the claims sought." *Id.* at 1213. The court went on to state, "what is relevant *depends on the facts*, and the facts here are that Amgen has not enabled *preparation of DNA sequences* sufficient to support its all-encompassing claims." *Id.* at 1213. (emphasis added). Again, as in *In re Fisher*, the focus is on what applicants, or one of ordinary skill in the art could do. The court focused on whether the preparation of the DNA sequences, within the scope of the claims, could *be prepared.* The application at issue was filed on November 30, 1984 and claimed priority to an application filed on December 13, 1983. Therefore, the "facts" relevant to the "preparation of DNA sequences" in the courts mind were

those that existed in 1983. Chemical synthesis of DNA was still only able to routinely produce short oligonucleotides. In short, one of the most important technological advances for the "preparation of DNA sequences" in a manner without "undue experimentation", highly efficient automated DNA synthesis, was still years away.

In *Hormone Research Foundation v. Genentech, Inc.* 904 F.2d 1558, 1568-69 (Fed. Cir. 1990) the court reversed a summary judgement for lack of enablement regarding claims directed to human growth hormone. The lower court had ruled that the alleged infringer had presented sufficient evidence indicating that the application was not enabled to merit summary judgement. (*Hormone Research Foundation v. Genentech, Inc.*, 708 F.Supp 1096 (N.D.Cal. 1988)). The Federal Circuit remanded this issue for further adjudication because the lower court had failed to adequately address the analysis of *In re Hogan*, 559 F.2d 959 (CCPA 1977) and *United States Steel Corp. v. Phillips Petroleum Co.* 865 F.2d 1247 (Fed. Cir. 1989).[2] In commenting on the relevance of these cases the *Hormone Research Foundation* court stated,

> It is unclear whether the high degree of potency and purity contemplated by the district court's analysis of enablement was influenced by the *potency and purity obtainable through recombinant DNA methodology*. Moreover, it is unclear from the record before us *whether that technology existed at the time the application was filed*. Further factual development as to the *state*

[2] In *In re Hogan* 559 F.2d 595 (CCPA 1976), the court addressed whether a priority application was enabled for a broad genus claim, even though art subsequent to the filing date of the application indicated that more research was needed to produce specific species within the genus claim. The court ruled, that the requirements of 35 U.S.C. § 112 must be addressed through the eyes of one of ordinary skill in the art at the time the application was filed, not after. At the time the priority application was filed, those of ordinary skill in the art would have seen the claim for what it is, an enabled, pioneering invention. The court reiterated this idea in *United States Steel Corp. v. Phillips Petroleum Co.*, 865 F.2d 1247 (Fed. Cir. 1989) which dealt with the same applications at issue in *In re Hogan*, now in the context of infringement. The court stated, "In sum, in determining sufficiency of support it is the state of the art . . . [at the time of the application] and the level of skill in the art at that time that is critical." *Id.* at 1252.

> *of the art at the date of the application* . . . is required for this court to review the enablement issues.

Id. at 1568-1569. (emphasis added).

The meaning and intent of the court is clear: one must assess the question of enablement in the light of the knowledge of one of ordinary skill in the art *at the time the application is filed.* Knowledge gained after the application is filed can not be used to prove the insufficiency of the application (see *In re Hogan* and *United States Steel Corp. v. Phillips Petroleum Co.*) and as was pointed out in *Hormone Research Foundation,* enablement cannot be addressed without looking at the *skill in the art at the time of the filing of the application.*

A central issue in the above cases is the level of predictability in the art.[3] The question remains, however, as to what "unpredictability" means. The courts have concluded that biological and chemical inventions are unpredictable, or at least they were, and what this means is often misconstrued. One of the least contested standards in patent law is that enablement issues are viewed through the lens of "undue experimentation". All enablement factors relating to the teaching of how to make and how to use a claimed invention are compared to whether "undue experimentation" is required. The question of predictability is no different. For example, the court in *In re Vaeck* 947 F.2d 497 (Fed. Cir 1991) addressed the issue of unpredictability by stating, "we do *not* imply that patent applications in art areas currently denominated as unpredictable must never be allowed generic claims encompassing more than the particular species disclosed in their specification." *Id.* at 496. (emphasis contained in original). The court went on to state that "there must be sufficient disclosure . . . to teach those of ordinary skill how

[3] See for example, In re Fisher stating, "In cases of involving unpredictable factors , such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the unpredictability of the factors involved." Id. at 838-39.

to make and how to use the invention . . ." *Id.* at 496. The question remains, what is a sufficient disclosure for an application that is in an "unpredictable" art? The clear answer given by the court was "the disclosure must adequately guide the art worker to determine, *without undue experimentation*, which species among all those encompassed by the claimed genus possess the disclosed utility. *Id.* at 496. (emphasis added). The court did **not** state, "without any experimentation," they stated "without undue experimentation". It is unequivocal from this statement that the court viewed predictability through the lens of "undue experimentation". This means that a standard of "predictability" that excludes "all" experimentation is simply incorrect.

"Unpredictability" is often used as a sword by the PTO to slash the scope of a legitimate biotechnology claim. The sharpness and size of this sword, however, are unduly exaggerated because of the misapplication of what is and should be "predictable". In the area of functional variants, such as discussed in *In re Fisher* or *Amgen Inc., v. Chugai Pharmaceutical Co.,* the standard when assessing whether the specification enables one of ordinary skill in the art to make and use the claimed variants is whether it would require "undue experimentation" to determine which variants are functional. In the language of *In re Vaeck*, "the disclosure must adequately guide the art worker to determine, *without undue experimentation*, which species among all those encompassed by the claimed genus possess the disclosed utility. *Id.* at 496.

Variants of tissue factor are enabled and described.

The Examiner has asserted "because the specification provides only a general method of producing tissue factor deletion and/or substitution variants, it does not provide a written description of *specific* tissue factor variants." No legal basis for this assertion has been presented and it is contrary to the cases on protein variants that the Federal Circuit has ruled on.

The applicants have provided ample instruction on the making and using of protein variants in general and specifically for tissue factor. One of ordinary skill in the art in 1987 (the time of the priority application) would have been able to make variant tissue factor proteins without undue experimentation. The standard set forth in *In re Fisher* and in *Amgen* by the Federal Circuit clearly indicates that one is to assess the enablement of protein variants in the context of whether it would require undue experimentation to make and test the claimed variants. In the present case the applicants have taught how to make the variants and there is abundant disclosure on the assays one would use to determine if the variants possessed activity. (see Examples 4 and 5). It would not require undue experimentation as defined by the Federal Circuit in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988) to make the claimed tissue factor variants. In fact *Wands* is a shining example of the Courts position that testing of the claimed molecules to find those that function as desired is not undue experimentation. In *Wands* the Federal Circuit upheld claims drawn to methods where monoclonal antibodies needed to be produced to practice the method. The issue before the court was the unpredictability of producing monoclonal antibodies and whether this was undue experimentation. The court was unconcerned that some attempts at producing an antibody might fail or that not all antibodies produced would meet the requirements of the claim. The court stated, "Wands carried out this entire procedure three times, and was successful each time in making at least one antibody that satisfied all of the limitations of the claim." *Id.* at 740. Thus, what was important was the fact that "some" antibodies within the claim were produced each time the complete method for making them was performed. The routine screening to find those that fell within the claim, was not undue experimentation. This is analogous to the protein variants claimed by the applicant. It

is irrefutable that there will be protein variants that function as tissue factor. Just as in *Wands* the experimentation needed to define those proteins is not undue.

The Examiner's argument that each and every variant is not described is without legal basis. The claims here are defined by protein molecules, not DNA molecules. There is no requirement that each and every embodiment of a claim be specifically described in the application. Amino acids 1 to 219 are described in the application. There is no requirement that every possible embodiment encompassed by the comprising language of claims 31-41 be specifically described. What is required is that human tissue factor including amino acids 1-219 be adequately described and as discussed above, this is described.

Claims 20-29 are not required to specifically describe the specific embodiments of the claim that stop, for example, at amino acid 224. What is required is that the application describe a human tissue factor protein including amino acid sequence between 219 and 263, which is clearly done (see above). The application teaches one of ordinary skill in the art how to make and test any tissue factor variant that is covered by claims 20-29. There is no requirement that each and every embodiment be described and the Examiner has not cited any case law that holds that claims generally drawn to multiple embodiments must describe each embodiment specifically.

For all of the above reasons, applicants assert that claims 4-6, 8, 20, 21, 23-25, 27-29, 31-36, and 38-41 are described and supported by the specification such that the description requirement of 35 U.S.C. § 112, first paragraph, is satisfied.

Rejections under 35 U.S.C. § 102

Claims 31 and 37 were rejected under 35 U.S.C. § 102(b) over Broze et al., "Purification of Human Brain Tissue Factor", J. Biol. Chem. 260(20) 10917-20 (1985). This rejection is respectfully traversed.

Claim 31 and 37 are drawn to recombinant human tissue factor. It is undisputed to one of ordinary skill in the art that recombinantly produced proteins do not have the same glycosylation patterns or purification contaminants as proteins that are produced from non-recombinant DNA molecules, such as those disclosed in Broze et al. There is ample support in the specification indicating that recombinantly produced proteins are different than naturally occurring proteins. (for example see page 7:lines 1-10).

Broze discloses the *putative* purified human tissue factor, but in reality if tissue factor was indeed present, it was present with at least one other contaminant because the amino acid sequence of the N-terminus reported by Broze was *wrong*. A comparison of the N-terminal sequence reported by Broze et al. and the confirmed N-terminal sequence reported by the Applicants is shown in Table 1, below. In addition, the N-terminal sequence reported by Bach et al., is also included.

Table 1

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Broze et al.	Ser-X	-Asn-Thr-Val-Ala-Val-Tyr-X								-Tyr-X		-leu-Lys-(Ser)-Lys-Asn-Phe.					
Applicant	Ser-Gly-Thr-Thr-Asn-Thr-Val-Ala-Ala-Tyr-Asn-Leu-Thr-Trp - Lys-Ser-Thr.																
Bach et al.	Ser-Gly-Thr-Thr-Asn-Thr-Val-Ala-Ala-Tyr- (?) -Leu-Thr-Trp - Lys-Ser-Thr																

Table 1 clearly indicates that the sequence reported by Broze et al. is very different than the sequence reported by both the Applicant and by Bach et al. Thus, the preparation of purified protein disclosed by Broze et al., is not limited to the sequence of human tissue factor protein at best and does not even contain any human tissue factor protein in the worst case scenario.

Allowance of claims 20, 21, 23, 24, 25, 27, 28, 29, and 31-41, is earnestly solicited.

Respectfully submitted,

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I hereby certify that this Amendment and Response to Office Action, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Patrea Pabst

Date: November 24, 1998